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| 09/778,290 | 02/07/2001 | Michael G. Wyllie | PC10325AAKM | 8690 |

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| JONES, DWAYNE C | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1614 | |

DATE MAILED: 02/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/778,290 | WYLLIE, MICHAEL G. | |
| | Examiner | Art Unit | |
| | Dwayne C Jones | 1614 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *28 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *29-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *28JAN2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Claims*

1. Claims 29-39 are pending.

2. Claims 29-39 are rejected.

3.

### *Response to Arguments*

4. Applicant's arguments filed January 28, 2004 have been fully considered but they are not persuasive. Applicants present the following arguments. First, applicant alleges that Ukimura does not teach of treating benign prostate hyperplasia or it symptoms. Second, applicant alleges that Hieble et al. teach away from the instant invention by stating that muscarinic antagonists should not be used in patients with outlet obstruction.

5. First, applicant alleges that Ukimura does not teach of treating benign prostate hyperplasia or it symptoms. The instant rejection is made over Hieble et al. in view of Ukimura. Accordingly, the prior art reference of Hieble et al. teach that one of the symptoms of benign hyperplasia causes an increased resistance to the flow of urine, (see Hieble et al. page 274s). The skilled artisan is here provided with motivation to treat the symptoms of benign hyperplasia causes an increased resistance to the flow of urine. Ukimura et al. provide examples of pharmaceutical agents that are used to increase the resistance to the flow of urine, namely alpha-adrenoceptor antagonists with muscarinic receptor antagonists.

6. Second, applicant alleges that Hieble et al. teach away from the instant invention by stating that muscarinic antagonists should not be used in patients with outlet obstruction. This allegation is disputed because the prior art reference of Hieble et al. teach that one of the symptoms of benign hyperplasia causes an increased resistance to the flow of urine, (see Hieble et al. page 274s). This allegation is directed to the data obtained from purinergic receptors, (see page 287s, 1st paragraph). Hieble et al. do teach that muscarinic receptor antagonists are used to treat urge incontinence, (see paragraphs 2 and 3 on page 287s). Combining this statement of using muscarinic receptor antagonists with the teaching that one of the symptoms of benign hyperplasia causes an increased resistance to the flow of urine, the skilled artisan is provided with the motivation to use muscarinic receptor antagonists with alpha-adrenoceptor antagonists, especially in view of *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

### *Information Disclosure Statement*

7. The information disclosure statement filed on January 28, 2004 has been reviewed and considered, see enclosed copy of PTO FORM 1449.

### *Claim Rejections - 35 USC § 112*

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 29-33, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and oxybutynin as well as structurally related compounds for each respective antagonist, does not reasonably provide enablement for other types of alpha-adrenoceptor antagonists and muscarinic antagonists that are not structurally related to the ones listed in claims 34 and 36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The instant invention is directed to treating lower urinary tract symptoms associated with benign hyperplasia. The method comprises administering the functional groups of alpha-adrenoceptor antagonists and muscarinic antagonists.

(2) The state of the prior art

The compounds of the inventions are administering the functional groups of alpha-adrenoceptor antagonists and muscarinic antagonists. However, the prior art does not teach that these compounds possess these types of properties to treat lower urinary tract symptoms, see Hieble et al..

(3) The relative skill of those in the art

The relative skill of those in the art of pharmaceuticals is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. Supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re Fischer, 427 F.2d 833, 839, 166 USPQ 10, 24 (CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. For example, in Ex Parte Sudilovsky, the Court

held that Appellant's invention directed to a method for preventing or treating a disease known as tardive dyskinesia using an angiotensin converting enzyme inhibitor involved unpredictable art because it concerned the pharmaceutical activity of the compound. 21 USPQ2d 1702, 1704-5 (BDAI 1991); In re Fisher, 427 F.2d 1557, 1562, 29 USPQ, 22 (holding that the physiological activity of compositions of adrenocorticotropic hormones was unpredictable art0; In re Wright, 999 F.2d 1557, 1562, 29 USPQ d, 1570, 1513-14 (Fed. Cir. 1993) (holding that the physiological activity of RNA viruses was unpredictable art); Ex Parte Hitzeman, 9 USPQ2d 1821, 1823 (BDAI 1987); Ex Parte Singh, 17 USPQ2d 1714, 1715, 1716 (BPAI 1990). Likewise, the physiological or pharmaceutical activity of alpha-adrenoceptor antagonists and muscarinic antagonists prior to filing of the instant invention was an unpredictable art. In addition, these terms do not predict the effectiveness or compatibility of future compounds that fall under the umbrella of the functional titles of alpha-adrenoceptor antagonists and muscarinic antagonists.

(5) The breadth of the claims

The instant claims are very broad. For instance, claim 29 is directed to the plethora of compounds of the functional titles of alpha-adrenoceptor antagonists and muscarinic antagonists. The breadth of claims was a factor in Amgen v. Chugai Pharm. Co., 927 F.2d 1200, 18 USPQ2d (Fed. Cir.),cert. Denied, 502 U.S. 856 (1991). In the Amgen case, the patent claims were directed to DNA sequences that encoded amino acid sequences. Because a very small change in the amino acid sequence of a protein

can result in a very large change in the structure-function activity of a protein and because the laws of protein folding are in such a primitive state, predicting protein structure (and hence, activity) while knowing only the sequence of the protein is akin to predicting the weather for a date in the future.

(6) The amount of direction or guidance presented

The amount of guidance or direction needed to enable the invention is inversely related to the degree of predictability in the art. In re Fisher, 839, 166 USPQ 24. Thus, although a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, in cases involving unpredictable factors, such as most chemical reactions and physiological activity, more teaching or guidance is required. In re Fischer, 427 F.2d 839, 166 USPQ 24; Ex Parte Hitzeman, 9 USPQ 2d 1823. For example, the Federal Circuit determined that, given the unpredictability of the physiological activity of RNA viruses, a specification requires more than a general description and a single embodiment to provide an enabling disclosure for a method of protecting an organism against RNA viruses. In re Wright, 999 F.2d 1562-63, 27 USPQ2d 1575. In the instant case, given the unpredictability of the physiological or pharmaceutical activity of the functional titles of alpha-adrenoceptor antagonists and muscarinic antagonists to be effective in treating lower urinary tract symptoms is insufficient for enablement. The specification provides no guidance, in the way of enablement for *** other than the alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-

pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and oxybutynin as well as structurally related compounds for each respective antagonist. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S. 5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

(7) The presence or absence of working examples

As stated above, the specification discloses alpha-adrenoceptor antagonists and the muscarinic antagonists that have the ability to treat lower urinary tract symptoms

associated with benign prostate hyperplasia. However, the instant specification only has enablement for the alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and oxybutynin as well as structurally related compounds for each respective antagonist.

(8) The quantity of experimentation necessary

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the compounds present and future that are embraced by the functional descriptions of all compounds described broadly as alpha-adrenoceptor antagonists and the muscarinic antagonists that would be enabled in this specification.

10. Claims 29-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. Claims 29-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

12. *Regents of the University of California v. Eli Lilly & Co.., 119 F.3d 1559, 1568 (Fed. Cir. 1997), cert. denied, 523 U.S. 1089, 118 S.Ct. 1548 (1980),* holds that an adequate written description requires a precise definition, such as by structure, formula, chemical name, or physical properties, "not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly, 119 F.3d at 1566.* The Federal Circuit has adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for *Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001)*, which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics, "including, inter alia, "functional characteristics when coupled with a known or disclosed correlation between function and structure...." *Enzo Biochem, Inc. v. Gen-Probe., 296 F.3d, 316, 1324-25 (Fed. Cir. 2002)* (quoting Guidelines, 66 Fed. Reg. At 1106 (emphasis added)). Moreover, although *Eli Lilly* and *Enzo* were decided within the factual context of DNA

sequences, this does not preclude extending the reasoning of those cases to chemical structures in general. *Univ. of Rochester v. G.D. Searle & Co., 249 F. Supp.2d 216, 225 (W.D.N.Y 2003).*

13. There is insufficient descriptive support for the phrases alpha-adrenoceptor antagonists and muscarinic antagonists. In addition, the instant specification does not describe what is meant by the phrases alpha-adrenoceptor antagonists and muscarinic antagonists other than the alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and oxybutynin as well as structurally related compounds for each respective antagonist. Structural identifying characteristics of the phrases alpha-adrenoceptor antagonists and muscarinic antagonists are not disclosed except for those of alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and oxybutynin as well as structurally related compounds for each respective antagonist. There is no evidence that there is any per se structure/function relationship between the phrases alpha-adrenoceptor antagonists and muscarinic antagonists other than those disclosed, namely the alpha-adrenoceptor antagonists of 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl)quinazoline, doxazosin, tetrazosin, abanoquil, prazosin, and indormain and the muscarinic antagonists of darifenacin, tolterodine, and

oxybutynin as well as structurally related compounds for each respective antagonist. The instant specification does provide an adequate written description for the phrases alpha-adrenoceptor antagonists and muscarinic antagonists. Accordingly, these claims fail to comply with the written description requirement.

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 29-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear as to what is meant by the phrase, "symptoms associated with benign prostate hyperplasia." The artisan is not provided with a clear understanding as to what is meant by this phrase. This renders the claims vague and indefinite.

***Claim Rejections - 35 USC § 103***

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

18. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

19. Claims 29-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hieble et al. in view of Ukimura. Hieble et al. teach that one of the symptoms of benign hyperplasia causes an increased resistance to the flow of urine, (see Hieble et al. page 274s). Hieble et al. also disclose of treating the lower urinary tract condition with an alpha-adrenoceptor antagonist, (see page 274s). Ukimura teaches of the administration of alpha-adrenoceptor antagonists with muscarinic receptor antagonists for the treatment of lower urinary tract conditions, (see abstract). In fact, Ukimura teaches of using the alpha-adrenoceptor antagonist of prazosin and the muscarinic receptor antagonist of oxybutynin to increase bladder capacity, (see page 258). Since is known in the art that one of the symptoms of benign hyperplasia causes an increased resistance to the urethral outflow of urine, it would have been obvious to the skilled artisan to combine these pharmaceuticals to treat the very same ailment that affects the

lower urinary tract. In addition, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . .[T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. C. Jones whose telephone number is (571) 272-0578. The examiner can normally be reached on Mondays, Tuesdays, Thursday, and Fridays from 8:30 am to 6:00 pm.

The official fax No. for correspondence is (703) 872-9306.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, may be reached at (571) 272-0584.

Wayne C. Jones
PRIMARY EXAMINER
Tech Ctr. 1614
February 9, 2004